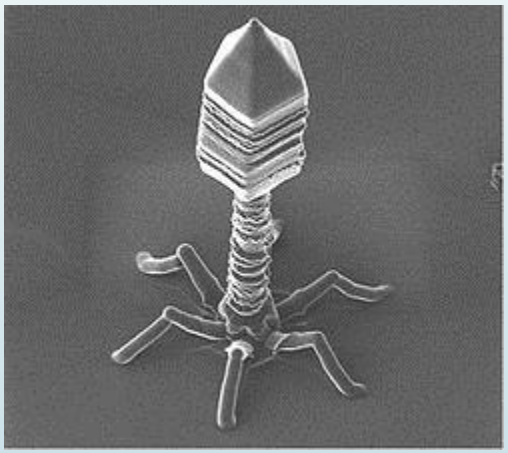
IN THE NAME OF GOD

Qazvin university of medical science
Department of Immunology & Microbiology
Journal Club & MSc Seminar

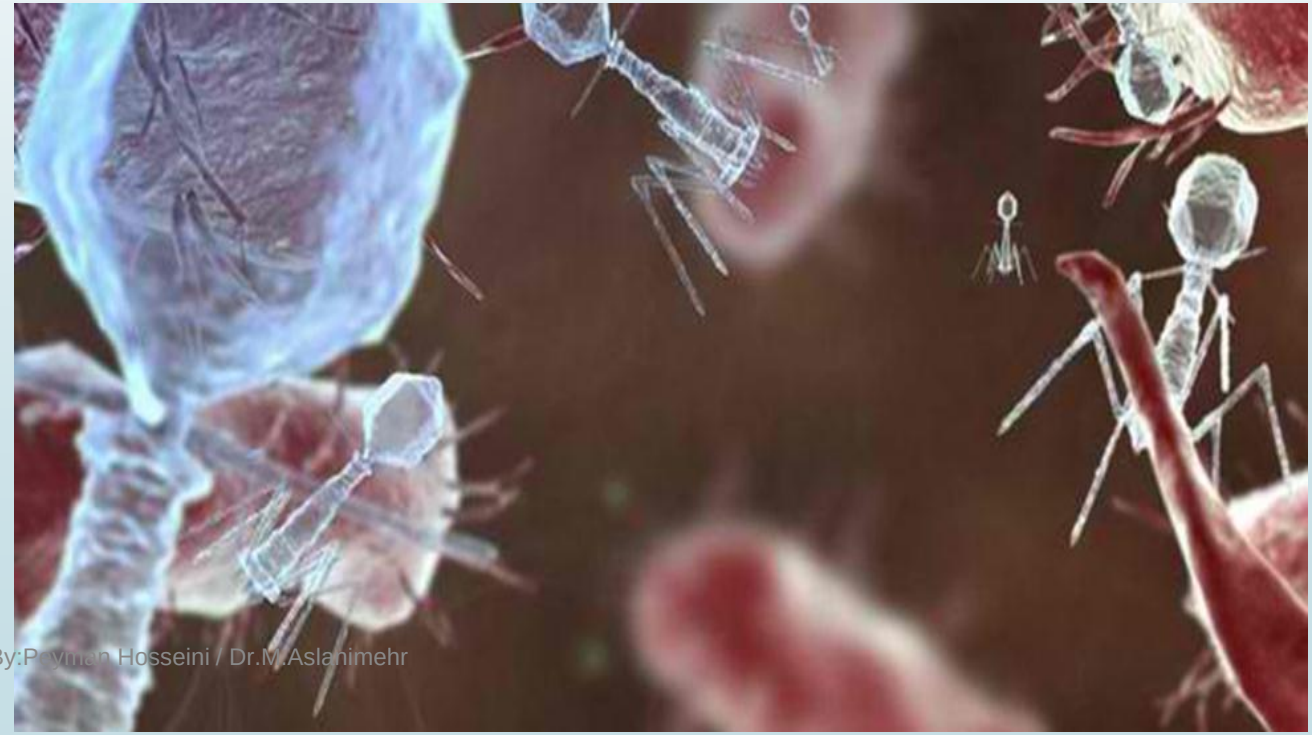
Phage therapy



Presented by : Peyman Hosseini
Supervised by : Dr.M. Aslanimehr

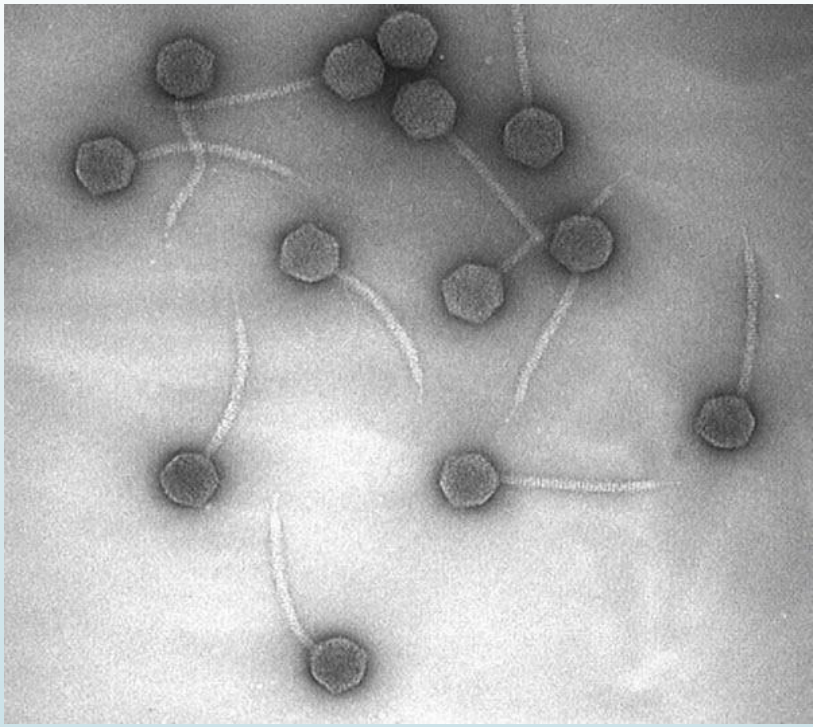
Introduction

- Bacteriophage (phage) are obligate intracellular parasites that multiply inside bacteria by making use of some or all of the host biosynthetic machinery



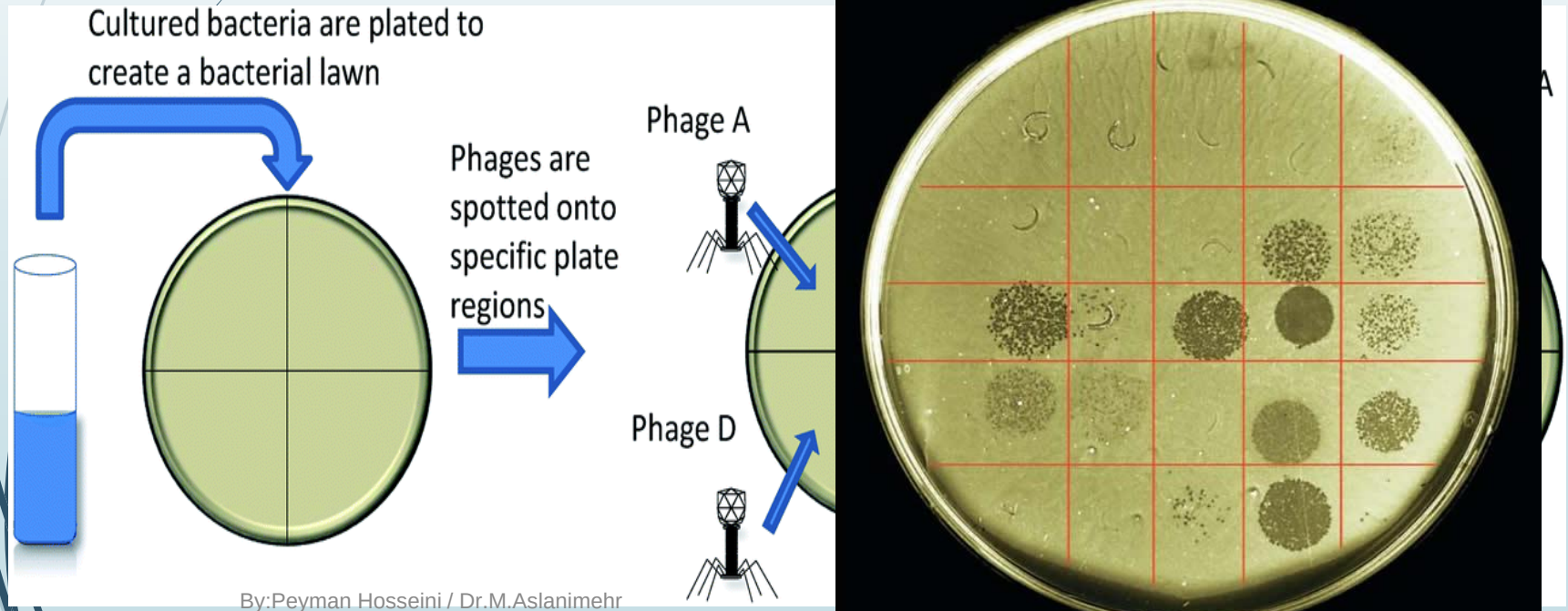
Introduction

- There are many similarities between bacteriophages and animal cell viruses. Thus, bacteriophage can be viewed as model systems for animal cell viruses. In addition a knowledge of the life cycle of bacteriophage is necessary to understand one of the mechanisms by which bacterial genes can be transferred from one bacterium to another.



Introduction

- Bacteriophage are used in the diagnostic laboratory for the identification of pathogenic bacteria (phage typing)



Introduction

- phage typing is not used in the routine clinical laboratory, it is used in reference laboratories for epidemiological purposes
- Recently, new interest has developed in the possible use of bacteriophage for treatment of bacterial infections and in prophylaxis

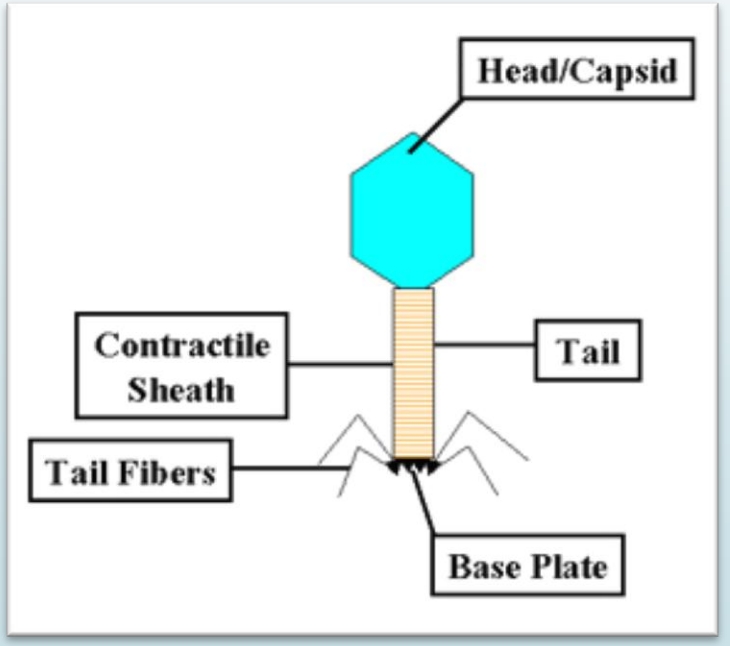




STRUCTURE OF BACTERIOPHAGE

- Structure
  - Bacteriophage come in many different sizes and shapes
  - 1. Size - T4 is among the largest phages; it is approximately 200 nm long and 80-100 nm wide. Other phages are smaller. Most phages range in size from 24-200 nm in length

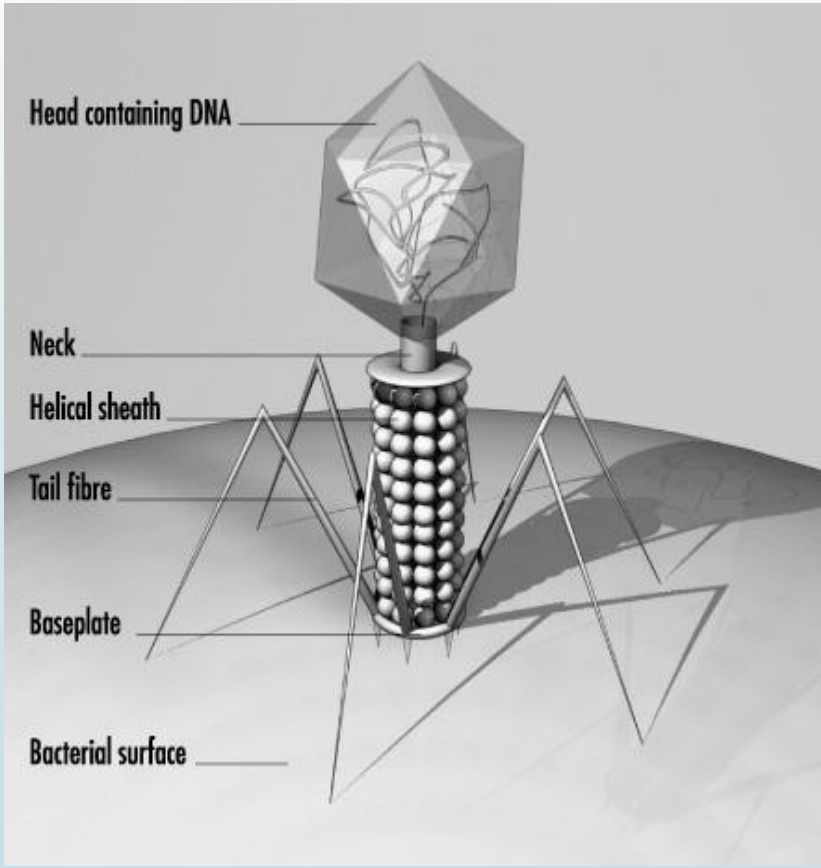
The basic structural features of bacteriophages



depicts the phage called T4

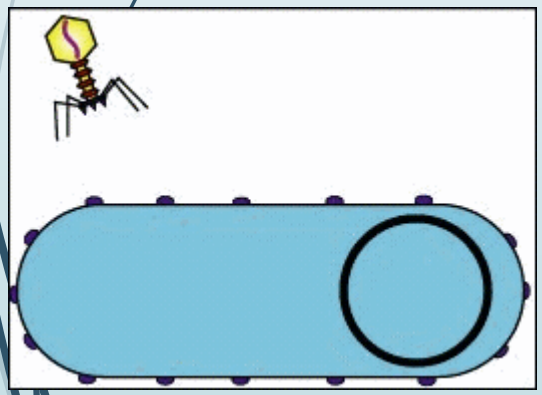
STRUCTURE OF BACTERIOPHAGE

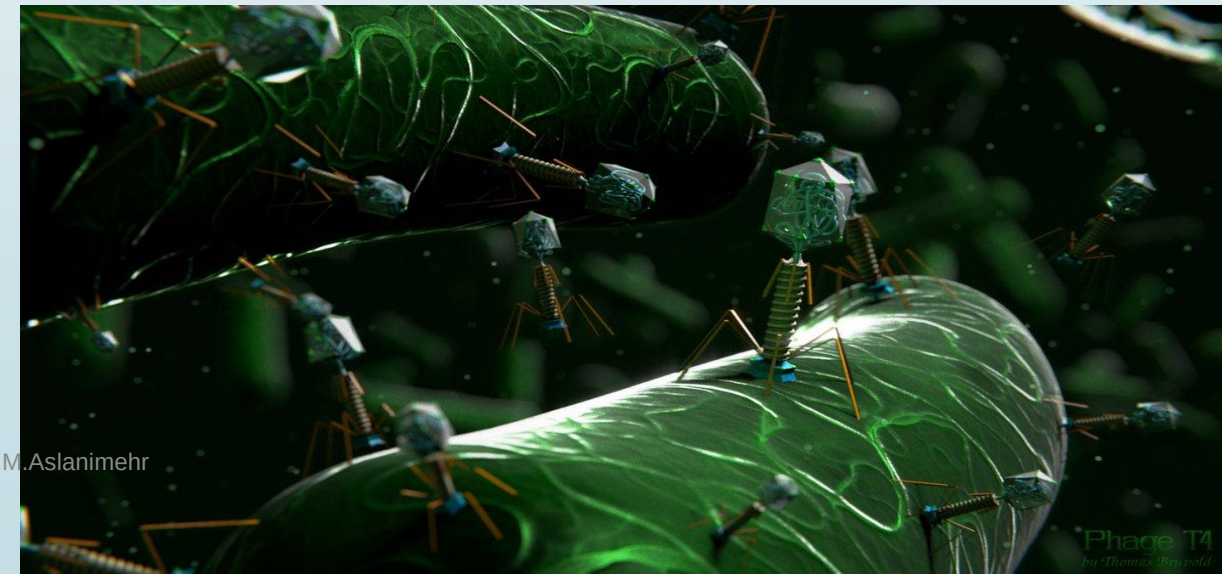
- 1. Tail-envelope not the phages contain a head structure which can vary in size and shape. Some are icosahedral (20 sides) others are filamentous.
- 2. The head contains nucleic acid
- 3. All the phages contain a tail structure which can be contractile or non-contractile. The tail fibers are hollow tubes through which the nucleic acid passes during infection of the bacterium
- 4. The tail fibers are composed of many copies of one or more different proteins. Inside the head is found the nucleic acid. The head acts as the protective covering for the nucleic acid.



INFECTION OF HOST CELLS

- A. Adsorption
  - The first step in the infection process is the adsorption of the phage to the bacterial cell. This step is mediated by the tail fibers or by some analogous structure on those phages that lack tail fibers and it is reversible

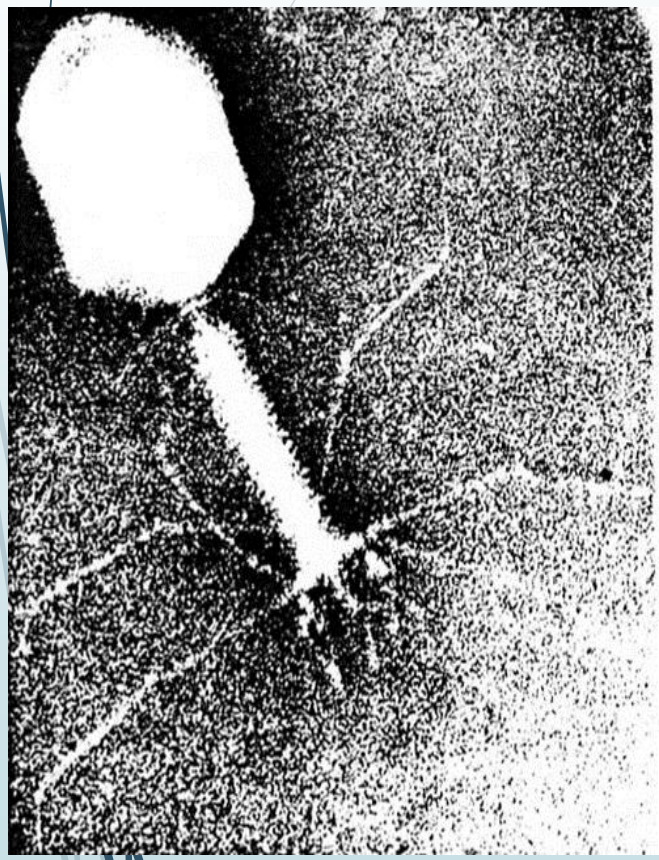


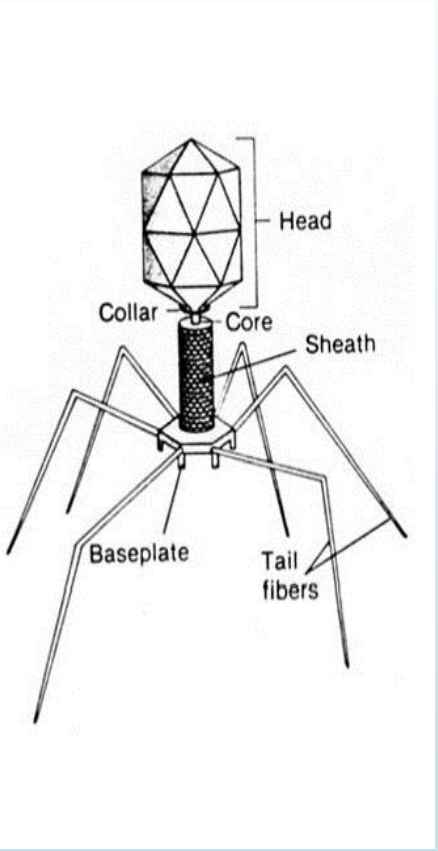


INFECTION OF HOST CELLS

- The tail fibers attach to specific receptors on the bacterial cell. The nature of the bacterial receptor varies for different bacteria
- Examples include proteins on the outer surface of the bacterium, LPS, pili, and lipoprotein. These receptors are on the bacteria for other purposes and phage have evolved to use these receptors for infection

INFECTION OF HOST CELLS

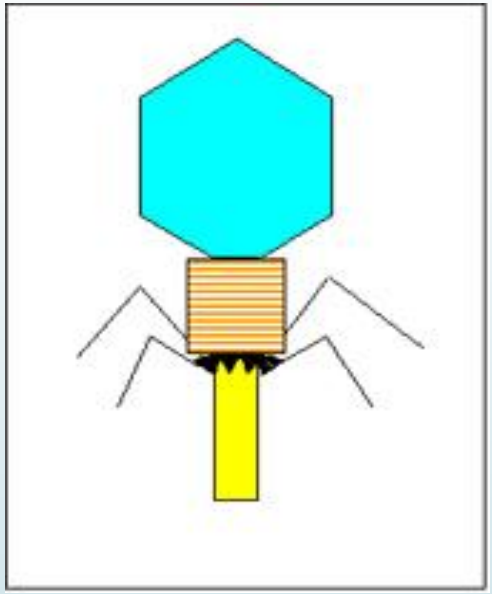




- B. Irreversible attachment
  - The attachment of the phage to the bacterium via the tail fibers is a weak and is reversible. Irreversible binding of phage to a bacterium is mediated by one or more of the components of the base plate. Phages lacking base plates have other ways of becoming tightly bound to the bacterial cell

INFECTION OF HOST CELLS

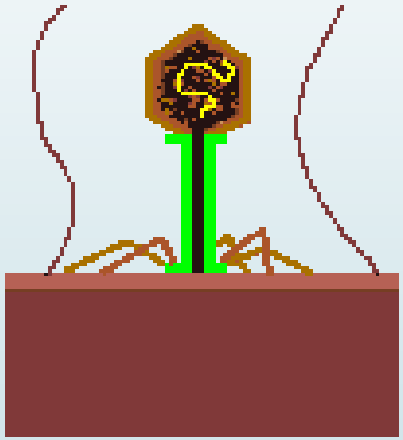
- C. Sheath Contraction
  - The irreversible binding of the phage to the bacterium results in the contraction of the sheath and the hollow tail fiber is pushed through the bacterial envelope



  - Phages that don't have contractile sheaths use other mechanisms to get the phage particle through the bacterial envelope. Some phages have enzymes that digest various components of the bacterial envelope

INFECTION OF HOST CELLS

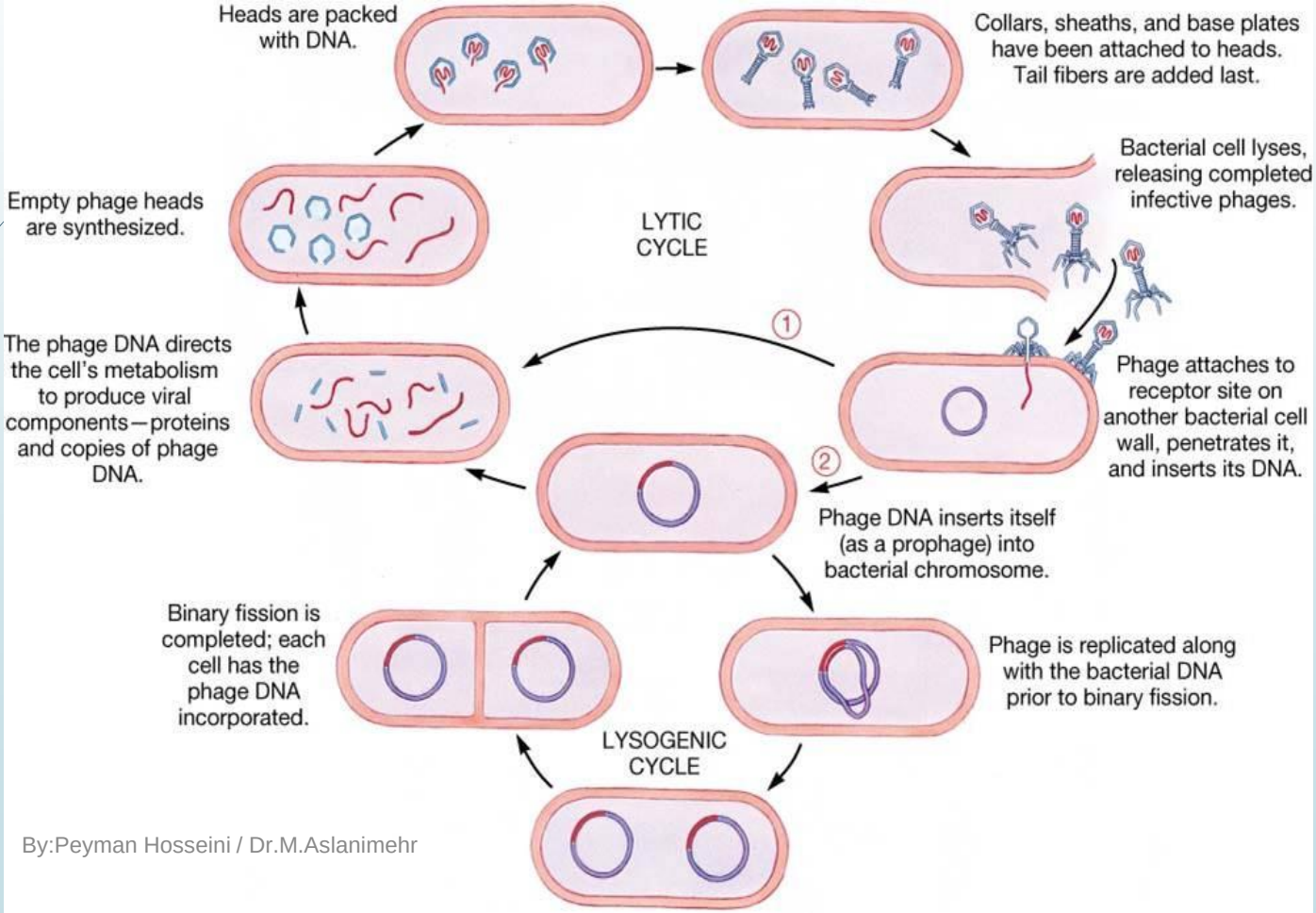
- D. Nucleic Acid Injection
  - When the phage has gotten through the bacterial envelope the nucleic acid from the head passes through the hollow tail and enters the bacterial cell. Usually, the only phage component that actually enters the cell is the nucleic acid.



INFECTION OF HOST CELLS

- The remainder of the phage remains on the outside of the bacterium. There are some exceptions to this rule. This is different from animal cell viruses in which most of the virus particle usually gets into the cell. This difference is probably due to the inability of bacteria to engulf materials.

PHAGE MULTIPLICATION CYCLE



By:Peyman Hosseini / Dr.M.Aslanimehr

PHAGE MULTIPLICATION CYCLE

- **A. Lytic or Virulent Phages**
  - 1. Definition
    Lytic or virulent phages are phages which can only multiply on bacteria and kill the cell by lysis at the end of the life cycle
  - 2. Life cycle
  - a. Eclipse period
    During the eclipse phase, no infectious phage particles can be found either inside or outside the bacterial cell. The phage nucleic acid takes over the host biosynthetic machinery and phage specified m-RNA's and proteins are made. There is an orderly expression of phage directed macromolecular synthesis, just as one sees in animal virus infections

PHAGE MULTIPLICATION CYCLE

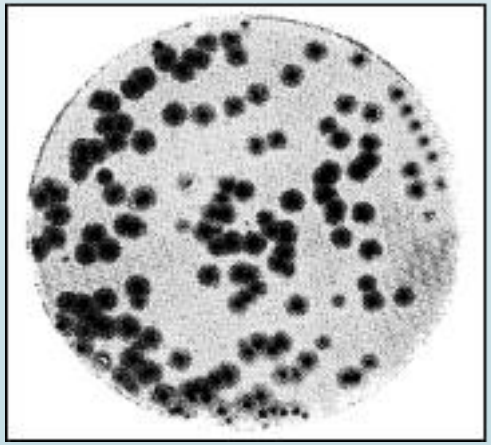
- Early m-RNA's code for early proteins which are needed for phage DNA synthesis and for shutting off host DNA, RNA and protein biosynthesis. In some cases the early proteins actually degrade the host chromosome. After phage DNA is made late m-RNA's and late proteins are made. The late proteins are the structural proteins that comprise the phage as well as the proteins needed for lysis of the bacterial cell

PHAGE MULTIPLICATION CYCLE

- b. Intracellular Accumulation Phase
  In this phase the nucleic acid and structural proteins that have been made are assembled and infectious phage particles accumulate within the cell.
- c. Lysis and Release Phase
  After a while the bacteria begin to lyse due to the accumulation of the phage lysis protein and intracellular phage are released into the medium. The number of particles released per infected bacteria may be as high as 1000

PHAGE MULTIPLICATION CYCLE

- Assay for Lytic Phage
  - Plaque assay
    Lytic phage are enumerated by a plaque assay. A plaque is a clear area which results from the lysis of bacteria (Figure 4). Each plaque arises from a single infectious phage. The infectious particle that gives rise to a plaque is called a PFU (Plaque Forming Unit)



PHAGE MULTIPLICATION CYCLE

- **B. Lysogenic or Temperate Phage**
  - Definition
    Lysogenic or temperate phages are those that can either multiply via the lytic cycle or enter a quiescent state in the cell. In this quiescent state most of the phage genes are not transcribed; the phage genome exists in a repressed state. The phage DNA in this repressed state is called a prophage because it is not a phage but it has the potential to produce phage

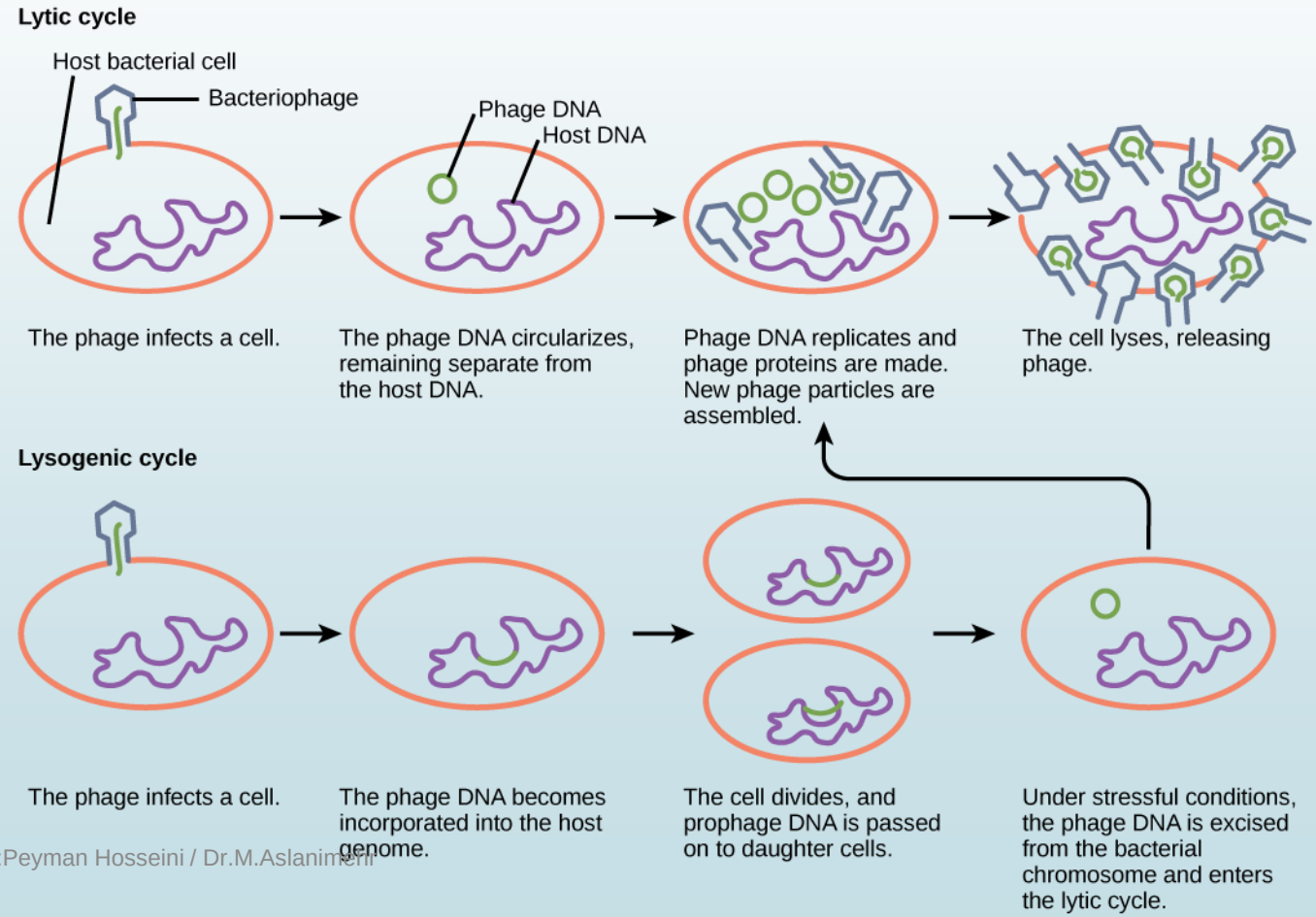
PHAGE MULTIPLICATION CYCLE

- In most cases the phage DNA actually integrates into the host chromosome and is replicated along with the host chromosome and passed on to the daughter cells. The cell harboring a prophage is not adversely affected by the presence of the prophage and the lysogenic state may persist indefinitely. The cell harboring a prophage is termed a lysogen

PHAGE MULTIPLICATION CYCLE

- **Events Leading to Termination of Lysogeny**
  - Anytime a lysogenic bacterium is exposed to adverse conditions, the lysogenic state can be terminated. This process is called induction. Conditions which favor the termination of the lysogenic state include: desiccation, exposure to UV or ionizing radiation, exposure to mutagenic chemicals, etc. Adverse conditions lead to the production of proteases (rec A protein) which destroy the repressor protein. This in turn leads to the expression of the phage genes, reversal of the integration process and lytic multiplication.

PHAGE MULTIPLICATION CYCLE



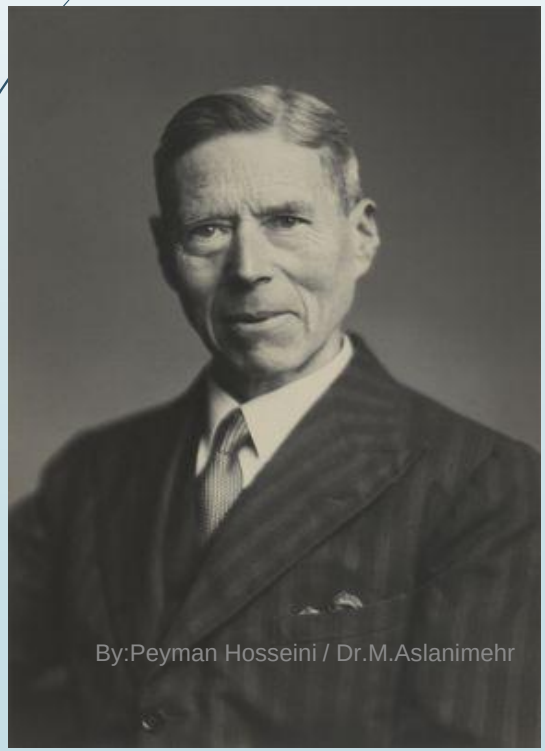
PHAGE MULTIPLICATION CYCLE

- **Lytic vs Lysogenic Cycle**
  - The decision for lambda to enter the lytic or lysogenic cycle when it first enters a cell is determined by the concentration of the repressor and another phage protein called *cro* in the cell. The cro protein turns off the synthesis of the repressor and thus prevents the establishment of lysogeny. Environmental conditions that favor the production of cro will lead to the lytic cycle while those that favor the production of the repressor will favor lysogeny.

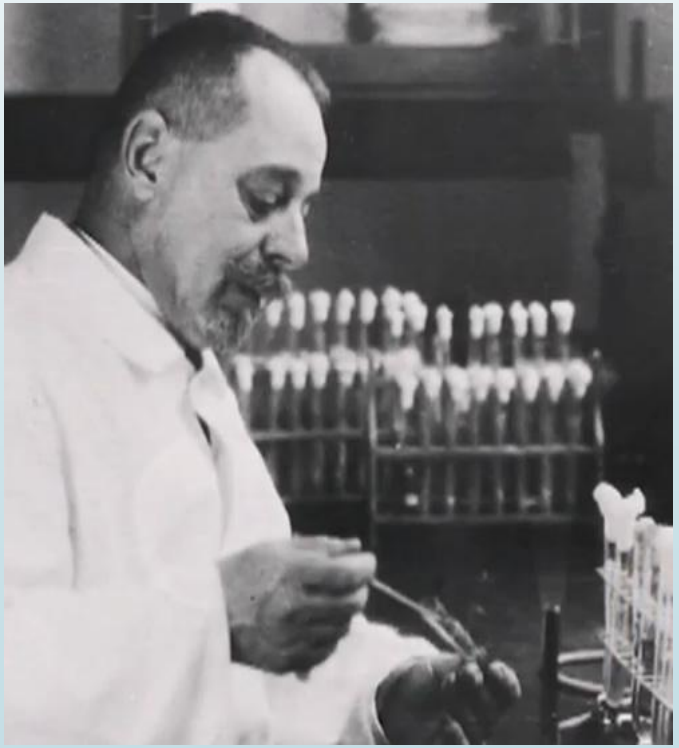
Phage therapy

- Bacteriophages were **discovered** by two people:

the English bacteriologist
Frederick Twort in 1915



the French-Canadian microbiologist
Felix d'Herelle in 1917



Phage therapy

- Immediately after their discovery, the thought of using phages to fight bacterial infections was already apparent
- D'Herelle began testing the therapeutic effects that phages may have on chickens and cows first and the tests were successful

Phage therapy

- human tests were conducted and the development of phage therapy became more extensive especially with the foundation of the Eliavia Institute in 1923

The **George Eliava Institute** of Bacteriophage, Microbiology and Virology, has been active since the 1930s in the field of phage therapy

Phage therapy

- the pharmaceutical company Eli Lilly began the commercialization of phage therapy in the US during the 1940s

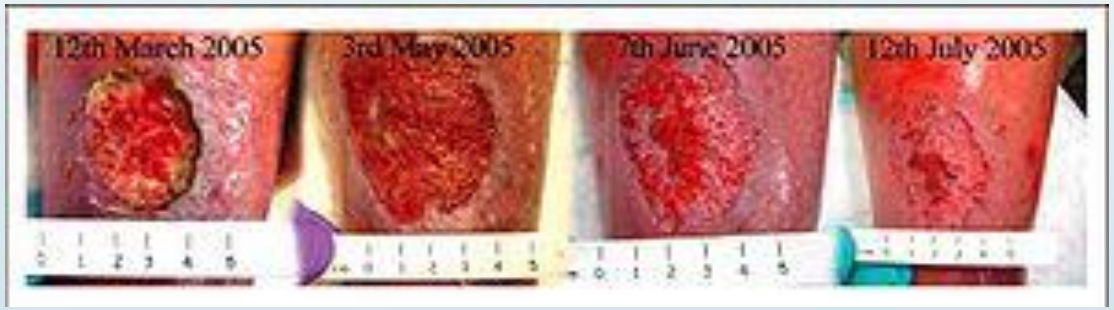
- During the Second World War, phages were used to treat bacterial diseases among soldiers of the Soviet Union, particularly gangrene and dysentery

Phage therapy

- The development of antibiotics in the 1950s led to a temporary setback on phage therapy as the use of antibiotics became more favourable. However, there has been a renewed interest in the development and employment of phage therapy in more applications

Delivery to targeted bacteria

- When phages were first discovered and applied in a clinical setting for the treatment of diseases, they were injected in the vicinity of the infection



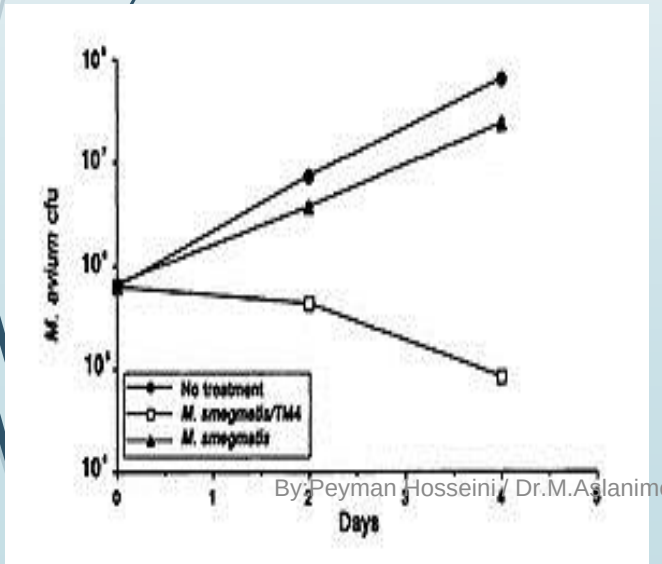
Venous leg ulcers infected with drug-resistant Pseudomonas and treated with bacteriophages over 5 months

Delivery to targeted bacteria

- Later mechanisms of delivery included
  - topical administration 3 times a day,
  - eye drops
  - orally before meals

Delivery to targeted bacteria

- Phages, unlike many antibiotic molecules, are not diffusible across membranes and must therefore have a method of delivery to the target cells
  - the best delivery mechanism may lie in using other nonpathogenic species of bacteria to bring the phage to its pathogenic target



The effect of treatment of Mycobacterium avium infected macrophages with Mycobacterium smegmatis 48 hours after infection (with and without the TM4 lytic phage) on number of intracellular M. avium

Delivery to targeted bacteria

- Some researchers have categorized different delivery modes as 'passive' and 'active‘
  - Passive delivery is achieved by administering large doses of phage that likely exceed how many bacteria are present
  - Active delivery, on the other hand, involves making sure that the phage lives long enough to generate progeny cells which will then kill the bacterial cells

Medical Uses

- Not long after his discovery, d'Herelle used phages to treat dysentery
- the first reported application of phages to treat infectious diseases of humans came from Bruynoghe and Maisin in France in 1921. They used phages to treat staphylococcal skin disease

Historical Medical Uses for Phage Therapy

- Anthrax
- Bubonic plague
- Cholera
- Dysentery
- Enteritis
- Gas gangrene
- Gastrointestinal infections
- Gonorrhea
- Lung and upper respiratory tract infections
- Meningitis
- Purulent infections in burn patients
- Staphylococcal skin diseases (e.g., boils, carbuncles, furuncles)
- Tuberculosis
- Typhoid fever
- Various bacterial infections (e.g., abscesses, mastoid infections, suppurating wounds, vaginitis)

Medical Uses

- d'Herelle used various phage preparations to treat thousands of patients having cholera and/or bubonic plague in India
- As late as the 1940s, Eli Lilly was producing seven phage products for human use, including preparations targeted against staphylococci, streptococci, *E. coli,* and other bacterial pathogens
- were used to treat various infections, including abscesses, suppurating wounds, vaginitis, acute and chronic infections of the upper respiratory tract, and mastoid infections

Medical Uses

- phages have also been used to treat anthrax, enteritis caused by *Campylobacter* species, *Clostridium difficile* gastrointestinal infections, gas gangrene, meningitis caused by *Haemophilus influenzae,* lung infections caused by *Klebsiella pneumoniae,* tuberculosis, gonorrhea, opportunistic infections of the lung caused by *Proteus* organisms, purulent infections related to *Pseudomonas aeruginosa* colonizationin burn patients, typhoid fever, and bacterial dysentery caused by *Shigella* species

Comparison to antibiotics

- Though phage therapy aims to do the same thing as antibiotics in treating bacterial infections, they have different mechanisms and therefore different associated advantages and disadvantages

Bacteriophages vs. Antibiotics

Advantages

- Very specific (affect only targeted bacterial species)
- Replicate at the site of infection
- Occur naturally (easy to locate)
- Safe (no reports of serious adverse effects)
- Active against antibiotic-resistant bacteria

Disadvantages

- Additional research required (lack of studies)
- Development of phage resistance and phage-neutralizing antibodies
- Not accessible to intracellular pathogens
- Difficult to administer (special training required)
- Can transfer toxin genes between bacteria

Advantages

- One advantage of phage therapy is that phages cannot grow without their target bacteria
- Another advantage is they would be easy to administer orally, intravenously, or topically
- Phages are also more host-specific than antibiotics
- Phages also work quickly. One study of mice infected with Vancomycin-resistant *Enterococcus faecium* found that if phage was injected 45 minutes after infection, 100% of the mice were saved

Advantages

- The specificity of phages makes them less toxic than some antibiotics
- Antibiotics also kill many of the bacteria that normally live on the human body (normal flora)
- phages are highly specific they will not harm our cells or the normal flora, which allows us to use them in much higher concentrations

Advantages

- phages are viruses they are readily cleared out of our bodies by our immune system
  - This prevents them from accumulating in our bodies and possibly causing any long lasting toxicity, making phages even less toxic to our cells
  - This also presents the problem that phages can be prevented from doing their job by being cleared out by our immune system
  - This is why the majority of phage cocktails are applied directly to wounds so they won't enter the blood stream and activate the immune system

Advantages

- Some bacteriophages synthesize enzymes that allow the breakdown of these biofilms so that the interior cells can be reached and lysed
- Bacterial resistance to phages is also less of a concern than resistance to antibiotics
  - Even if resistance develops to a bacteriophage, finding a phage that will still work against that bacteria would only take a couple of days
- Another major advantage is that bacteriophages are cheap to produce and the years of experimentation in Russia and Georgia have shown almost no side effects at all

Disadvantages

- For example, though they would be easy to administer orally, this may lead to a need to neutralize the stomach acid before ingesting in order to minimize damage to the phage or to the delivery bacteria, which may not be able to survive at such a low pH
- For the intravenous application of bacteriophages, they may be cleared by the human immune system which would recognize them as foreign and a possible threat
- The phage would also need to be highly purified so that there is no dangerous contaminant or toxin going into the patient's circulatory system

Disadvantages

- The fact that bacteriophages are so strongly specified for their bacterial target, though in some ways an advantage, can also serve as a disadvantage
  - this is because the exact bacteria must be diagnosed in order to use the right kind of phage. Antibiotics, on the other hand, affect a wider range of bacteria, so an exact diagnosis is not essential

Comparison to antibiotics

Bacteriophages	Antibiotics	Comments
Very specific (i.e., usually affect only the targeted bacterial species); therefore, dysbiosis and chances of developing secondary infections are avoided	Antibiotics target both pathogenic microorganisms and normal microflora. This affects the microbial balance in the patient, which may lead to serious secondary infections.	High specificity may be considered to be a disadvantage of phages because the disease-causing bacterium must be identified before phage therapy can be successfully initiated. Antibiotics have a higher probability of being effective than phages when the identity of the etiologic agent has not been determined.
Replicate at the site of infection and are thus available where they are most needed	They are metabolized and eliminated from the body and do not necessarily concentrate at the site of infection.	The "exponential growth" of phages at the site of infection may require less frequent phage administration in order to achieve the optimal therapeutic effect.
No serious side effects have been described.	Multiple side effects, including intestinal disorders, allergies, and secondary infections (e.g., yeast infections) have been reported	A few minor side effects reported for therapeutic phages may have been due to the liberation of endotoxins from bacteria lysed in vivo by the phages. Such effects also may be observed when antibiotics are used
Phage-resistant bacteria remain susceptible to other phages having a similar target range	Resistance to antibiotics is not limited to targeted bacteria	Because of their more broad-spectrum activity, antibiotics select for many resistant bacterial species, not just for resistant mutants of the targeted bacteria
Selecting new phages (e.g., against phage-resistant bacteria) is a relatively rapid process that can frequently be accomplished in days or weeks.	Developing a new antibiotic (e.g., against antibiotic-resistant bacteria) is a time-consuming process and may take several years	Evolutionary arguments support the idea that active phages can be selected against every antibiotic-resistant or phage-resistant bacterium by the ever-ongoing process of natural selection

microbial biotechnology

Microbial Biotechnology (2011) 4(5), 643–650 doi:10.1111/j.1751-7915.2011.00259.x

Evaluation of lytic activity of staphylococcal bacteriophage Sb-1 against freshly isolated clinical pathogens

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Introduction

During the last decades, a dramatic worldwide increase of antibiotic-resistant *Staphylococcus aureus* infections was observed (Ayliffe, 1997; Chambers, 1997; Herold *et al.*, 1998; Cosgrove *et al.*, 2003). The CDC estimates that 80 000 hospitalized patients experienced a nosocomial infection with methicillin-resistant *S. aureus* (MRSA) every year. Alternative treatment options to antibiotics are therefore urgently needed. One potential treatment option for antibiotic-resistant *S. aureus* is lytic bacteriophages, which naturally infect *S. aureus* (Merril *et al.*, 1996; Barrow and Soothill, 1997; Carlton, 1999; Chanishvili *et al.*, 2001; Duckworth & Gulig, 2002; Inal, 2003; Bruttin and Brussow, 2005; Merril *et al.*, 2006) known as phage therapy. Phages, unlike antibiotics, are specifically targeted to a particular bacterial species and thus spare bystander bacteria from other species lytic damage. Phages thus much less affect the balance of normal microflora than antibiotics. The G. Eliava Institute of Bacteriophages, Microbiology and Virology (Tbilisi, Georgia) was the first centre, where therapeutic phage cocktails targeting various bacterial pathogens were developed. Several cocktails were for many decades successfully used against *S. aureus* in Georgian hospitals (Chanishvili and Sharp, 2008; Kutateladze and Adamia, 2008).

In 1977, L. Kvachadze isolated a particularly active phage from an Eliava Institute phage cocktail used to treat staphylococcal infections. The phage isolate was named Sb-1 and its properties were described in Russian/Georgian publications (Andriashvili *et al.*, 1981; Ackermann and Abedon, 2001). Sb-1 is particularly well suited for phage therapy. It is a strictly 'virulent' phage, i.e. it propagates exclusively by lytic infections and does not establish a lysogenic state. 'Virulent' phages in contrast to temperate phages do not carry bacterial pathogenicity genes. Sb-1 has a very broad host range on *S. aureus*, including antibiotic-resistant strains. Its genome was sequenced and no known virulence genes were identified. The sequence confirms also our previous observation that the Sb-1 genome includes no GATC sequences (Andriashvili *et al.*, 1986). which are the target of Sau3A, the major restriction enzyme found in many *S. aureus* strains. This article presents a further characterization of Sb-1, its genome map, biological properties, host range against a broad panel of clinical isolates including MRSA strains, and sample clinical data including a case report of its successful application against a chronic *S. aureus* infection in a cystic fibrosis patient.

Pulsed field gel electrophoresis analysis

A coverage of greater than 98% is exceptional for a single phage isolate. Therefore we controlled whether the high coverage of Sb-1 phage was the consequence of a collection containing closely related *S. aureus* strains. We explored the diversity of our *S. aureus* strain collection by investigating 54 of the 352 isolated by pulsed field gel electrophoresis (PFGE). Visual analysis of the PFGE results identified 25 distinct restriction pattern. The isolates could be classified into nine multi-strain branches by unweighted-pair group method using average linkages (UPGMA) dendrogram analysis (Fig. 4A). One branch of group 1 was represented by 16 isolates. The other branches were represented by at most four different isolates. Antibiotic resistance pattern of 54, genotyped bacterial strains showed that bacteria reveal high resistance to polypeptides, β-lactames, bacitracin and aminoglycosides (Table 1).

Table 1. Percentage of antibiotic resistance of genetically different clinical *Staphylococcus aureus* strains.

PFGE groups	Bacterial strain	β-Lactames	Aminoglycosides	Tetracycline	Macrolides	Chloramphenicol	Polypeptides	Ciprofloxacin	Methicillin	Bacitracin
G1	16	100	68.7	37.5	68.7	25	100	50	6.25	100
G2	2	100	100	50	100	50	100	50	0	100
G3	2	100	50	0	0	0	100	0	0	100
G4	4	100	100	75	75	50	100	75	25	100
G5	3	100	100	33.3	66.6	0	100	100	0	100
G6	2	100	100	50	50	50	100	100	50	100
G7	2	50	100	100	100	50	100	100	0	100
G8	4	50	100	75	50	75	100	75	0	100
G9	3	33.3	100	66.6	0	33.3	100	33.3	33.3	66.6
Individual	16	93.75	75	37.5	43.75	31.25	100	62.5	43.75	87.5
Total	54	88.8	81.4	44.4	55.5	29.6	100	61.1	20.3	94.4

Sample clinical applications

For many years, the Eliava Institute in Tbilisi was producing a staphylococcal phage preparation which was effectively used locally (topically). In late 1970s, the Institute scientists elaborated a method for construction of the phage for intravenous use. In the series of experiments, therapeutic effectiveness was studied to treat different infectious diseases, including acute and chronic sepsis, peritonitis, osteomyelitis, mastitis, purulent arthritis, acute and chronic lung abscesses, chronic pneumonia and bronchitis, bronchoectasis, purulent cysts and others. Sb-1 phage was the key component of the therapeutic preparation.

In some cases when the approved cocktails (commercial preparations) do not work *in vitro* aga
gen isolated from patient's samples, we
'autophage' against patient's specific ba
these phages for treatment of the patient.
example of current clinical application of S

Subsequent to phage therapy, the general condition of patient improved. Most notably, the follow-up of the *S. aureus* level in the sputum showed a steady decrease over 2 months until *S. aureus* slipped under the detection level after a month. In contrast *P. aeruginosa* levels showed comparative constancy during 12 months, but at the end of the observation period *P. aeruginosa* titres reached to $\times 10^5$ pfu ml^{-1}, but after therapy, no bacteria was found in the sputum.

The most important fact is that the use of antibiotics in the complex therapy was able to be decreased by 50%. However, no significant improvement has yet been seen in the X-ray and blood analyses. The patient is still under treatment.

commercially available Pyophage in patient with cystic fibrosis.

Case report. Patient M. Kh. was a 7-year-old girl suffering from cystic fibrosis diagnosed in 2002. The disease was confirmed by genetic analyses: she is homozygous for the mutation – **1677 deLTA**. The sweat test revealed a strongly elevated chloride concentration of 126–135 mmol l^{-1}. She showed a chronic colonization of the lungs with *Pseudomonas aeruginosa* and *S. aureus*. During several years, the patient was treated with broad spectrum antibiotics, but there was no effect on the *P. aeruginosa* and *S. aureus* colonization. The initial bacterial concentration (before phage application) in the patient's sputum was 1×10^7 cfu ml^{-1} for *S. aureus*, and the amount of *P. aeruginosa* remained minimal – 7×10^4 cfu ml^{-1}.

Phage treatment was
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The physician decided to add use of now well-characterized phage Sb-1, which had high lytic activity against the patient's specific culture *in vitro*. Sb-1 phage was added to the Pyophage cocktail and applied this augmented phage cocktail five times with a nebulizer to the patient. After the joint application (Pyophage with Sb-1 staphylococcal phage), the amount of *S. aureus* drastically decreased and during a medication-free month, the level of *S. aureus* remained fairly low, at about 10^3–10^5 cfu ml^{-1}; for *P. aeruginosa*, it was 10–100 cfu ml^{-1}. No adverse effects were seen in the patient upon application of the Sb-1 phage.

We examined the concentration of phages (staphylococcal and *P. aeruginosa*) in the patient's sputum during phage treatment. Three to four hours after phage application, phage was detected at 10^2 pfu ml^{-1}. On the second day, before the next phage application, no phage was detected in the sputum (Fig. 5).

Conclusion

Phage cocktails against pyogenic infections (Pyophage) have a long history of reportedly safe in the former Soviet Union. This phage cocktail is still today sold in Georgia and Russia as a registered over-the-counter medicine. However, since neither the phage preparation nor the clinical trials conducted with them were published in Western scientific journals, claims on their efficacy were seen with substantial scepticism by Western scientists. Here we demonstrate that *S. aureus* phage Sb-1 is a representative of the SPO1 group of Myoviridae, which can be considered as safe with respect to its genome sequence. The phage can be purified and showed a broad host range against large and representative *S. aureus* strain collections from different geographical areas, including MRSA strains. Phage resistance development is very low and largely reverts to sensitivity. A case study in a cystic fibrosis patient showed no adverse events of phage application in a nebulizer and a promising clinical response. Placebo-controlled double-blinded clinical trials are now warranted to test the value of Sb-1 phage against *S. aureus* infections in defined clinical situations.

Conclusion

- Bacterial resistance to antibiotics is a growing threat in our world. Though early studies of phage therapy did not produce consistently favorable results, there is reason to believe that with the enhanced understanding that we have of viral biology it is likely that bacteriophages can be a helpful therapeutic tool. Though many believe that phages will not replace antibiotics right away or maybe ever, there is definite potential for their use in conjunction with antibiotics


THANK
YOU!